The Health and Economic Impact of Substandard and Falsified Antimalarials in Myanmar

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Honors Thesis
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University of North Carolina at Chapel Hill

3/2/20

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Keywords

Antimalarial, quality, substandard, falsified, Myanmar

Word Count Abstract: 236, Text: 2973; Figures 1; Tables 2; References 51

Abstract

Significant efforts have been made in the fight against malaria in the greater Mekong subregion, but two-thirds of the population in Myanmar still reside in high-risk regions for malaria infections. Substandard and falsified antimalarial medications pose a threat to disease transmission, efforts to control antimalarial resistance, and eliminate malaria from the region. This study is the first to estimate the health and economic impact of substandard and falsified antimalarials in Myanmar. Malaria illness, care seeking and health outcomes were simulated using the Substandard and Falsified Antimalarial Research Impact (SAFARI) model, a probabilistic agent-based model. Myanmar-specific epidemiologic, demographic and cost inputs were extracted from existing literature. The total annual cost of malaria in Myanmar was estimated to be $14.084 (95% CI: $14.040-14.128) million, including $2.719 (95% CI: $2.715-2.722) million in direct costs. Substandard and falsified antimalarials contributed $2 million to the total annual, including $16,000 in direct costs. The model estimated that poor-quality antimalarials contributed to 33% of hospitalizations in Myanmar. In the event of widespread artemisinin resistance, we simulated an additional $550,000 in yearly costs. The presence of poor-quality antimalarials are hampering efforts to reduce malarial disease burden, control the spread of antimalarial resistance, and eliminate malaria in Myanmar and the greater Mekong subregion.

Introduction

Malaria is a preventable, infectious disease transmitted by mosquito-borne parasites. Most uncomplicated malarial cases treated with quality, first-line antimalarials in outpatient settings result in full recovery. However, inadequately treated symptomatic disease can quickly progress to complications such as anemia or neurologic sequelae, or result in death (World Health Organization, 2014b). In 2017, there were an estimated 435,000 deaths worldwide due to malaria (World Health Organization, 2018). While significant global efforts aimed at malaria over the last two decades have led to substantial decreases in malaria morbidity and mortality, the burden largely remains in poor countries (United Nations, 2015). In Southeast Asia, malaria incidence rates have decreased by more than 40% between 2010 and 2017, where many countries in the great Mekong subregion are working towards the goal to complete elimination by 2030 (World Health Organization, 2015a, 2015b, 2016, 2017, 2018). However, countries such as Myanmar still have two-thirds of its population residing in high risk regions for malaria infection.

One of the key challenges to malaria elimination in Southeast Asia is the emergence of malaria parasites that are resistant to effective medicines (World Health Organization, 2016, 2018). Resistance to artemisinin treatment was first reported in Cambodia in 2008, and has since been accompanied by resistance to artemisinin partner drugs, leading to higher failure rates of the most effective malaria drugs, artemisinin-based combination therapies (ACTs). Resistance to ACTs has now been detected in five countries in the greater Mekong subregion (Imwong, Hien, Thuy-Nhien, Dondorp, & White, 2017). Myanmar faces the largest malaria disease burden

within the subregion and has confirmed cases of *P. falciparum* resistance to ACTs (World Health Organization, 2015b, 2016, 2018).

Substandard and falsified antimalarials are ineffective or harmful and may be contributing to the emergence of resistance to artemisinin and ACTs (Nayyar, Breman, Newton, & Herrington, 2012; Ozawa et al., 2018; World Health Organization, 2017). The World Health Organization (WHO) defines substandard medications as products which fail to meet quality standards or lack sufficient Active Pharmaceutical Ingredient (API), and falsified medicines as products which "deliberately misrepresent their identity, composition, or source" (World Health Organization, 2017). Poor-quality antimalarials prolong illness, offer inadequate treatments, and increases the risk of adverse events and antimalarial resistance (Nayyar, et al., 2012; Ozawa, et al., 2018; World Health Organization, 2017). In Myanmar, studies have demonstrated that 0.0-39.2% of antimalarial drugs are substandard or falsified (Dondorp et al., 2004; Guo et al., 2017; Hajjou et al., 2015; Khin et al., 2016; P. Newton et al., 2001; P. N. Newton et al., 2008; Wondemagegnehu, 1999; Yong et al., 2015).

While poor-quality antimalarials may pose a significant threat towards national and international plans to control and eliminate malaria in Myanmar and Southeast Asia, their impact has not been estimated to date. The impact of substandard and falsified antimalarials have only been presented in Africa, where a sizable burden have been estimated (Beargie et al., 2019; Ozawa, Evans, Higgins, Laing, & Awor, 2019; Ozawa et al., 2019). Given the confirmed existence of parasite resistance, we sought to understand

the impact of poor-quality antimalarials in Myanmar to inform efforts to reach the 2030 malaria elimination targets.

Materials and Methods

We developed and applied the Substandard and Falsified Antimalarial Research Impact (SAFARI) model to examine the impact of poor-quality antimalarials in Myanmar. This model simulates malaria infection, patient care-seeking, disease progression, treatment outcomes, and associated costs. A detailed description of the model can be found in other publications (Beargie, et al., 2019; Ozawa, Evans, et al., 2019; Ozawa, Haynie, et al., 2019) and modifications specific to Myanmar are described here (Ozawa, Evans, et al., 2019). We first conducted a literature search for malaria and Myanmar to identify and utilize relevant accessible data. All model inputs are listed in Table 1. Key data sources we used included the vector borne disease control program (VBDC) report from the Myanmar Ministry of Health, WHO world malaria report, the ACTwatch outlet report, and the Demographic and Health Survey (DHS) for Myanmar, in addition to published literature. Key data inputs were simulated to vary probabilistically to account for natural variations in epidemiological and cost inputs. Epidemiological data were varied based on beta distributions and cost data were ranged using gamma distributions.

The model simulates 1,000 individuals of all ages with malaria due to *P. falciparum* and *P. vivax* parasites in a five-day period, accumulated over one-year. We then ran this model 10,000 times. Each modeled case of malaria represented around 24 real world cases in Myanmar. At the beginning of each five-day period, individuals with symptomatic malaria infection decided whether and where to seek care resulting in variations on medication use and disease

outcomes. At the end of the week, patients either became healthy, asymptomatic, died, or remained sick. Outcomes were tracked throughout the model year and averaged at the model. Sensitivity analysis to validate this method was conducted by increasing the ratio of modeled cases to actual cases and comparing the outputs to ensure no significant difference.

We modeled seven options for people to seek treatment for malaria: they could go to 1) public facilities, 2) private facilities, 3) pharmacies, 4) informal private sector (drug shops or itinerant drug vendors), 5) community health workers (CHWs), 6) self-treat, or 7) not seek care. Available stock of medications at each location based on national data of antimalarial market share determined the probability that patients received different types of treatment, such as ACTs, artemisinin monotherapy, chloroquine, primaquine, and others (e.g. sulfadoxine–pyrimethamine) (ACTwatch Group and Population Services International Myanmar, 2016). Current national treatment guidelines for uncomplicated cases of *P. falciparum* malaria in Myanmar include three ACTs: artemether lumefantrine (AL), dihydroartemisinin piperaquine (DHA-PPQ), or artesunate mefloquine (AS-MQ) (World Health Organization, 2015b). First-line treatment for radical cure of *P. vivax* malaria is chloroquine to treat blood stage parasites, accompanied by primaquine to treat latent liver stage parasites that can cause relapses (World Health Organization, 2015b).

Some individuals received no treatment due to a stock out based on data on frequency of stock outs of ACTs (ACTwatch Group and Population Services International Myanmar, 2016). Individuals who did not seek care or received no drug at a facility remained symptomatic into the next five-day period where they again had the chance to decide whether to seek care. Individual

treatment outcomes were determined based on the efficacy of the medicine they received, adjusted by medication quality (amount of API) and patients' modeled adherence. Adherence rates were obtained from a study assessing adherence to six-dose regimen of artemether-lumefantrine in Myanmar (Z. W. Tun et al., 2012).

Treatment efficacy was defined as medication-specific likelihood of adequate clinical and parasitological response at 28 days based on polymerase chain reaction (PCR) (Chu et al., 2018; Ejov, Tun, Aung, & Sein, 1999; Htun et al., 2017; Muhamad, Ruengweerayut, Chacharoenkul, Rungsihirunrat, & Na-Bangchang, 2011; Myint et al., 2017; Na-Bangchang, Ruengweerayut, Mahamad, Reungweerayut, & Chaijaroenkul, 2010; Nyunt et al., 2017; Phyo et al., 2011; Shwe, Lwin, & Aung, 1998; Frank Smithuis et al., 2006; Frank Smithuis et al., 2004; F. M. Smithuis et al., 2010; K. M. Tun et al., 2018; Yuan et al., 2015; Zwang et al., 2009). We incorporated substandard and falsified antimalarials based on prevalence by medicine from the literature, where poor quality antimalarials were assigned lower API concentrations found from studies testing antimalarials (Tabernero et al., 2015).

We used data from the VBDC report on the number of cases of severe malaria and malaria related hospitalizations to estimate probabilities that treated cases would progress to become severe (Department of Public Health, 2015). For untreated cases of malaria, we employed rates of progression to severe disease reported by a Delphi study (Lubell et al., 2011). Agents that sought care with severe malaria became hospitalized and received inpatient care. Severe malaria patients faced the probability of dying, resulting in neurologic sequelae, or fully recovering to become healthy. Rates of progression to neurologic sequalae or death were obtained from a study in Southeast Asia (Southeast Asian Quinine Artesunate Malaria Trial

(SEAQUAMAT) Group, 2005). Modeled results were scaled to the population of Myanmar based on the number of new cases simulated to estimate the annual malaria burden in the country.

Primary model outputs were estimates of health outcomes, direct costs and productivity losses. Direct costs included costs to patients such as transportation, testing, medication, consultation, and hospitalization costs, and costs to public facilities and CHWs for providing treatment (ACTwatch Group and Population Services International Myanmar, 2016; Naing and Gatton, 2004; World Health Organization, 2010). Indirect costs included productivity losses for care-seeking, disability, or premature death. Productivity losses were estimated using the human capital approach where lost earnings were calculated based on gross domestic product (GDP) per capita and duration of productivity losses (The World Bank, 2019). Care seeking productivity loss was estimated to be between three to five days of lost earnings, while lifetime productivity losses were calculated from the average age of death due to malaria until average life expectancy, discounted at 3% (Chen, Aung, Thant, Sudhinaraset, & Kahn, 2015). Disability productivity losses were estimated by applying the disability weights for neurologic sequelae to discounted lifetime productivity losses. All cost outputs were rounded to the nearest thousands and expressed in 2017 United States Dollars (USD).

We ran the simulation across three scenarios. The baseline scenario simulates the overall burden of malaria in Myanmar at current levels of antimalarial quality. A second scenario simulating no substandard and falsified antimalarials was compared to the

baseline to elucidate the health and economic impact of poor-quality antimalarials. Finally, a third scenario simulated hypothetical widespread ACT resistance in which the cure rate of ACTs was reduced to that of other antimalarials, and patients receiving ACTs experienced five more days of prolonged illness (Dondorp, et al., 2004; Khin, et al., 2016; Yong, et al., 2015). These scenarios were compared to baseline using unpaired two-sample t-tests.

Results

Table 2 presents the annual health and economic burden of malaria in Myanmar. Based on around 117,000 (95% CI: 116,982-117,018) cases of malaria per year, we estimated that malaria results in 899 (95% CI: 895-903) severe cases, 449 (95% CI: 447-452) hospitalizations, and 202 (95% CI: 201-203) deaths annually. Costs of care seeking and productivity losses added up to $14.084 (95% CI: $14.040-14.128) million annually, which consisted of $2.719 (95% CI: $2.715-2.722) million in direct costs and $11.365 (95% CI: $11.321-11.409) million in productivity losses. Direct costs included $2.2 million in care, $71,000 in medications, and $1,400 in testing. Productivity losses for care-seeking totaled $5.093 (95% CI: $5.086-5.099) million and lifetime productivity losses from disability or early death was estimated at $6.272 (95% CI: $6.229-6.316) million.

Substandard and falsified antimalarials contributed to 15 (3%) hospitalizations ($p < 0.001$) and 67 (33%) deaths ($p < 0.001$) annually. Moreover, substandard and falsified antimalarials accounted for 15% of the current economic impact of malaria in Myanmar estimated at $2.04 million ($p < 0.001$). The impact of poor-quality antimalarials consisted mainly of lifetime productivity losses accrued from premature death and disability. Direct costs were

estimated at around $16,000 annually ($p < 0.001$), including out-of-pocket costs to the patient and public facility costs for public facilities.

Our hypothetical scenario of antimalarial resistance reduced the effectiveness of ACTs and increased the duration of illness. This scenario resulted in a 3.6% increase in severe cases where 32 more malaria cases became severe each year ($p < 0.001$), leading to 16 (3.5%) more deaths annually ($p < 0.001$). The antimalarial resistance scenario increased the total economic burden of malaria $550,000 ($p < 0.001$). This additional cost due to antimalarial resistance consists of approximately $104,000 in direct costs and $442,000 in productivity losses.

Discussion

Our results demonstrate the need for Myanmar to ensure antimalarial quality in order to reduce the burden of malaria and reach 2030 malaria elimination targets. Based on the best available data, we estimated that substandard and falsified antimalarials currently contribute to 37% of the deaths each year with an impact of over $2 million annually, equivalent to around 2.9% of Myanmar's GDP (The World Bank). This is substantial as the country's total expenditure on health was 2.3% of GDP in 2014 in comparison (World Health Organization, 2014a). The burden of malaria could increase even further if the prevalence of poor-quality antimalarials continues and resistance to ACTs increase.

Poor-quality antimalarials directly hinder priorities outlined by Myanmar's National Plan for Malarial Elimination such as "interrupting transmission of and

eliminating *P. falciparum* malaria with special emphasis on areas of multi-drug and artemisinin resistance." Utilizing high-quality medicines leads to shorter and less severe illness, lending to fewer fatalities and less opportunity for spread of contagious diseases and accumulation of drug resistance (Bassat, Tanner, Guerin, Stricker, & Hamed, 2016). Antimalarial resistance and inability to achieve malarial elimination in Myanmar harm neighboring countries in the Greater Mekong Subregion (GMS) and risk the spread of resistance worldwide where the burden of malaria is even greater.

Our results are comparable to other estimates of modeled artemisinin resistance in the region. For example, Lubell et al. modeled artemisinin resistance in Cambodia in 2014 by assuming the efficacy of artemisinin would be reduced to 70%, resulting in a 28% increase in direct medical costs.(Lubell et al., 2014) In our model, a reduced efficacy of ACTs to 66% resulted in an increase of 4.3% in direct medical costs. Lower costs of care in Myanmar and difference in model structures explain these differences, where Lubell et al. used a simple decision tree as compared to our dynamic agent-based model, which incorporated variations in care-seeking and costs.

Compared to our model results from Africa, where we focused on the burden of malaria among children under age five, this analysis in Myanmar estimated the impact of malaria across all-ages. The malaria burden in Africa is vastly larger, with estimated cases of 200 million children in sub-Saharan Africa, where malaria tends to be more severe among children (World Health Organization, 2018). This analysis simulated 117,000 all-age cases in Myanmar given the target toward malaria elimination regardless of age.

Moreover, unique characteristics of disease epidemiology in the greater Mekong subregion makes it important to ensure treatment quality. The biting pattern of mosquitos in Myanmar, which mainly bite in the early evening before children go to bed, makes insecticide treated nets less effective in preventing malaria (F. M. Smithuis et al., 2013a; F. M. Smithuis et al., 2013b). Thus for Myanmar, the most effective tool against the further spread of malaria is early detection and proper use of effective antimalarials.

Unlike sub-Saharan Africa where malaria cases are mainly caused by the *P. falciparum* parasite, more than 30% of the malarial cases in Southeast Asia are caused by *P. vivax* parasites (World Health Organization, 2016, 2018). This epidemiological difference poses a unique challenge to elimination in the GMS, as *P. vivax* infections face higher rates of relapse. The life cycle of *P. vivax* parasites include dormant stages in liver cells which cause asymptomatic infection (World Health Organization, 2015b). This affects treatment effectiveness, where current recommended treatment is to include primaquine with chloroquine to prevent recrudescence. However, primaquine should not be given to people with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to the risk of red blood cell breakdown. G6PD deficiency is not easy to detect in low-resourced settings in Myanmar. While ACTwatch data demonstrated a need for increasing primaquine availability in rural Myanmar, primaquine would be ineffective in instances where 27% of chloroquine may be substandard and falsified (Khin, et al., 2016; Wondemagegnehu, 1999).

The main limitation of this study is the availability of quality data for model inputs. We conducted a literature review to utilize the most recent literature across inputs, but some data were older or had to be extrapolated across the region. Furthermore, current literature surrounding malarial treatment in Myanmar most commonly focused on migrant populations of Myanmar residents who are treated in bordering countries such as Thailand, which may not be reflective of the broader population. We chose conservative estimates in cases of conflicting or outdated information. Due to limited data availability, inputs for treatment efficacy, adherence, and utilization may not reflect the heterogeneity of practice amongst the urban/rural or high/low malaria transmission regions of Myanmar. Literature regarding availability of medicines in the public sector were unavailable. To address these data limitations, we varied our inputs probabilistically over 10,000 model runs to capture the uncertainty in model estimates.

Mitigating the impact of substandard and falsified antimalarials is important to lessen the current health and economic burden of malaria in Myanmar and meet future malaria elimination targets. Poor quality medicines not only prolong disease and lead to more severe cases, but also allow malaria to spread further, contributing to the burden of illness and facilitating the growth of antimalarial resistance. To make malaria elimination in Southeast Asia a reality, better surveillance and elimination of poor-quality antimalarials must be a greater priority.

Acknowledgments

We thank malaria experts, Steve Taylor and Jessica Lin who offered insights and feedback into model inputs. We also thank the Research and Scholarship in Pharmacy pathway course

directors at the Eshelman School of Pharmacy at the University of North Carolina and Kathryn Morbitzer for guidance and feedback.

Financial Support

No financial support was provided for this study.

Conflicts of Interest

The authors declare no conflicts of interest.

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Table 1. Key Model Inputs, Sources, and Assumptions

	Model Inputs	Point Estimates	Standard Deviation	Source
Demographic and Epidemiologic Data	Number of estimated cases	116772	182616	World Malaria Report 2018
	Proportion of cases that are *Pf*	0.68		WHO Fact Sheet 2010
	Proportion of cases that are *Pv*	0.31		WHO Fact Sheet 2010
	Proportion of malarial cases that were severe	0.0036	0.00044	Calculated from: VBDC 2015
	Average age of death from malaria	25		Chen 2015
	Life Expectancy	67		World Bank 2019
	Healthcare-seeking			DHS, assumed for all ages is same for children <5
	Public Facilities	0.334		
	Private Facilities	0.139		
	Pharmacy	0.027		
	Drugstore	0.074		
	CHW	0.028		
	Self/ Neighbors	0.261		
	No Treatment	0.136		
	Probability of testing			ACTwatch 2015
	Public Facilities	0.035		
	Private Facilities	0.025		
	Pharmacy	0.03		
	Drugstore	0.044		
	CHW	0.011		
Proportions of Medication Stock by Facility	Public facilities			ACTwatch 2015
	ACT	0.708		
	Chloroquine	0.223		
	Monotherapy	0.038		
	Other	0.031		
	Primaquine with ACT	0.58		
	Primaquine with Chloroquine	0.55		
	Private facilities			ACTwatch 2015
	ACT	0.6		
	Chloroquine	0.165		
	Monotherapy	0.133		

	Other	0.102	
	Primaquine with ACT	0.326	
	Primaquine with Chloroquine	0.338	
	Pharmacy		
	ACT	0.401	ACTwatch 2015
	Chloroquine	0.283	
	Monotherapy	0.2	
	Other	0.116	
	Primaquine with ACT	0.016	
	Primaquine with Chloroquine	0.02	
	Drugstore		
	ACT	0.392	ACTwatch 2015
	Chloroquine	0.290	
	Monotherapy	0.247	
	Other	0.071	
	Primaquine with ACT	0.015	
	Primaquine with Chloroquine	0.019	
	CHW		
	ACT	0.708	ACTwatch 2015
	Chloroquine	0.223	
	Monotherapy	0.038	
	Other	0.031	
	Primaquine with ACT	0.58	
	Primaquine with Chloroquine	0.55	
	Self/ neighbors		
	ACT	0.392	Assumption, same as Drugstore
	Chloroquine	0.290	
	Monotherapy	0.247	
	Other	0.071	
	Primaquine with ACT	0.015	
	Primaquine with Chloroquine	0.019	
Medication in-stock probabilities	Antimalarial in-stock probabilities		
	Public Facilities	0.83	ACTwatch 2015
	Private Facilities	0.76	

	Pharmacy	0.49		
	Drugstore	0.312		
	CHW	0.831		
	Self/ Neighbor	1		
Prevalence of Substandard and Falsified Antimalarials	Antimalarial in-stock probabilities			
	ACT	0.12		ACTwatch 2015
	Chloroquine	0.27		
	Monotherapy	0.18		
	Other	0.24		
	Primaquine	0		
Medication effectiveness	Probability of cure with quality-assured medicines			
	ACT	0.9798		Myint 2017, Na-Bangchang 2010, Nyunt 2017, Smithuis 2006, Smithuis 2004, Smithuis 2010, Tun 2018, Zwang 2009
	Chloroquine	0.9392		Nyunt 2017, Chu 2018, Ejov 1999, Htun 2017, Muhamad 2011, Phyo 2011, Yuan 2015
	Primaquine with ACT or Chloroquine	0.9770		Smithuis 2010, Chu 2018, Muhamad 2011, Yuan 2015
	Oral Artemisinin Monotherapy	0.8099		Chu 2018, Shwe 1998
	Other	0.6552		Smithuis 2004, Ejov 1999
	No Treatment	0		Assumption
Medication costs by facility	Public facilities			
	ACT	--		ACTwatch 2015
	Chloroquine	--		
	Primaquine	--		
	Monotherapy	--		
	Other	--		
	Private facilities			
	ACT	$0.18	$0.02	ACTwatch 2015
	Chloroquine	$0.10	$0.01	
	Primaquine	$0.04	$0.01	

	Monotherapy	$2.22	$0.52	
	Other	$0.48	$0.05	
	Pharmacy			
	ACT	$0.41	$0.04	ACTwatch 2015
	Chloroquine	$0.17	$0.05	
	Primaquine	$0.30	$0.06	
	Monotherapy	$2.48	$0.21	
	Other	$0.48	$0.05	
	Drugstore			
	ACT	$0.37	$0.04	ACTwatch 2015
	Chloroquine	$0.30	$0.03	
	Primaquine	$0.02	$0.04	
	Monotherapy	$3.18	$0.43	
	Other	$0.63	$0.06	
	CHW			
	ACT	--		ACTwatch 2015
	Chloroquine	--		
	Primaquine	--		
	Monotherapy	$2.66	$0.63	
	Other	--		
	Self/ Neighbor	--		
Non-medication costs	Cost per primary level hospitalization	$9.60	$4.72	WHO CHOICE 2010
	Average testing costs	$0.07	$0.05	Calculated from testing costs and market share of testing based on ACTwatch 2015
	Transportation costs	19.04 Kyat		Naing 2004
	Productivity loss per sick day	$3.42		Calculated from World Bank 2019 (GDP per capita/365)
	Discounted productivity loss per death	$30,368.30		Calculated from World Bank 2019 discounted at 3%

ACT = Artemisinin-based combination therapy; CHW = Community health workers; GDP = Gross domestic product; DHS = demographic and health survey; *Pf* = *P. falciparum*; *Pv* = *P. vivax*; USD = United States Dollar; VBDC = Vector borne disease control; WHO CHOICE = World health organization Choosing interventions that are cost effective; WMR = World malaria report

Table 2. Estimated Annual Health and Economic Impact of Substandard and Falsified Antimalarials in Myanmar

		Burden of Malaria		No Substandard and Falsified Antimalarials			Antimalarial Resistance		
		Baseline	**95% CI**	**Potential Savings**	**Percent Difference**	**P-value**	**Additional Costs**	**Percent Difference**	**P-value**
Health Impact	**Cases**	117,000	116,982 - 117,018	--	--	--	--	--	--
	Deaths	202	201 - 203	-15	-3.3%	<0.001	9	6.6%	<0.001
	Severe Cases	899	895 - 903	-23	-2.6%	<0.001	32	3.6%	<0.001
	Hospital-izations	449	447 - 452	-67	-33.1%	<0.001	16	14.5%	<0.001
Economic Impact†	**Total Annual Burden**	$14,084,000	$14,040,000 - $14,128,000	-$2,043,000	-14.5%	<0.001	$546,000	3.9%	<0.001
	Direct Costs	$2,719,000	$2,715,000 - $2,722,000	-$16,000	-0.6%	<0.001	$104,000	3.8%	<0.001
	Productivity Losses	$10,760,000	$10,699,000 - $10,822,000	-$2,049,000	-17.8%	<0.001	$442,000	3.9%	<0.001

CI = Confidence interval
†Rounded to nearest thousands